Synthetic Methods

DOI: 10.1002/anie.201201704

Preparation of Alkylmagnesium Reagents from Alkenes through Hydroboration and Boron–Magnesium Exchange**

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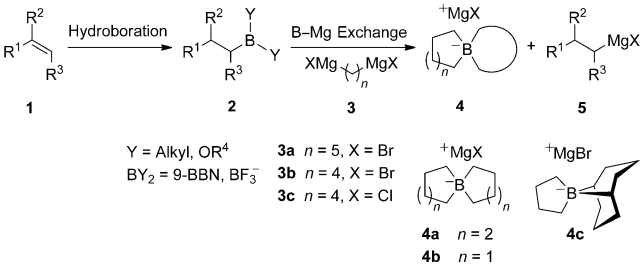
For more than 100 years organomagnesium compounds have been one of the most important synthetic tools for the construction of C–C bonds in both academia and industry.[1] However, their most important formation method, the direct synthesis by insertion of magnesium metal into the C–X bond of alkyl halides, involves highly reactive radical intermediates that may lead to undesired homocoupling products or other side reactions.[2] Unfortunately, these side reactions become more problematic with bulky alkyl groups, long alkyl chains, or substrates containing multiple protected functionalities.[3] Applications of alkylmagnesium reagents towards the later stages of a total synthesis are rare for two reasons. Firstly, they are incompatible with many functional groups which are likely to be present nearing the end of a synthesis. Secondly, alkyl halides are usually too reactive and often cannot be carried through many synthetic steps. Hence, alternative methods for the formation of alkylmagnesium reagents have been examined, such as hydromagnesiation[4] of olefins, a method that is synthetically useful only in special cases.[5] In contrast to alkylmagnesium reagents, mild methods for the formation of arylmagnesium reagents from aryl halides or heteroaryl compounds have been developed recently.[6]

In search for approaches to organometallic reagents through anti-Markovnikov functionalization of olefins, Knochel and co-workers have taken advantage of the high anti-Markovnikov selectivity of hydroboration.[7] Thus, dialkyl zinc reagents can be obtained efficiently through a sequence of hydroboration followed by a boron–zinc exchange reaction.[8] While organozinc reagents have been proven to be highly useful reagents for organic synthesis, their reduced nucleophilicity compared to organomagnesium compounds also sets limitations regarding their reactivity towards weaker electrophiles.[1,2a] Hence, it would be highly desirable to have a general method to generate alkylmagnesium reagents from alkenes by taking advantage of the high levels of regio- and stereocontrol in the course of the well-established functionalization of alkenes through hydroboration. A subsequent boron–magnesium exchange reaction could provide the corresponding alkylmagnesium reagents. However, this step is indeed problematic.[9]

Thus, early attempts to realize a boron–magnesium exchange reaction by addition of ordinary alkylmagnesium reagents to trialkylboranes **2** were not successful owing to incomplete transfer of the alkyl substituents from boron to magnesium.[10] A significant advance was reported by Murahashi and Kondo, who observed complete boron–magnesium exchange of trialkylboranes upon reaction with a 1,5-dimagnesium reagent (Scheme 1) with concomitant formation of the spiro[5,5]boron-ate[11] **4a** as the proposed byproduct.[12] However, the method suffers from three major limitations: First the method is limited to the generation of primary alkylmagnesium reagents starting from mono-substituted alkenes, because the boron–magnesium exchange reaction is inhibited owing to steric hindrance. Second, the method is restricted to the use of trialkylboranes. However, the use of the more stable alkyl boronic esters obtained through rhodium-catalyzed hydroboration would be highly desirable. Finally, this protocol requests a special diethyl ether/toluene solvent mixture for the boron–magnesium exchange reaction to proceed, which limits the synthetic utility of the resulting organomagnesium reagents significantly, most notably for applications in subsequent cross-coupling reactions.[13]



Scheme 1. Access to alkylmagnesium reagents from olefins through hydroboration and boron–magnesium exchange.

We herein report the development of a general method for the preparation of primary and secondary alkylmagnesium reagents from alkenes through hydroboration and boron–magnesium exchange and their use in a wide range of carbon–carbon bond forming reactions, including iron-, palladium-, and copper-catalyzed cross-coupling reactions as well as a stereospecific directed copper-mediated allylic substitution.

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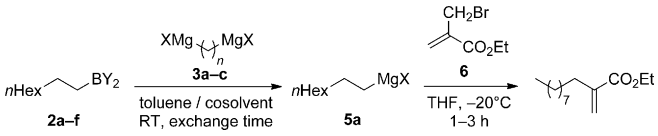
[**] This work was supported by the Fonds der Chemischen Industrie, the DFG (GRK 1038), the Krupp Foundation (Alfried Krupp Award for young university teachers to B.B.), and Novartis (graduate fellowship to M.A.R.). We thank M. Fritz for technical support and BASF SE for donations of chemicals (esp. borane reagents).

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201201704.

To accelerate the problematic boron–magnesium exchange reaction, we wondered whether the use of an 1,4-dimagnesium reagent may be beneficial owing to faster cyclization towards the corresponding spiro[4,4]boron-ate **4b** with concomitant liberation of the desired alkylmagnesium reagent (Scheme 1).

Indeed, after the boron–magensium exchange reaction of trioctylborane **2a** with dimagnesium reagents **3a** and **3b** by low-temperature ^{11}B NMR spectroscopy, we observed that formation of the corresponding spiro[4.4]boron-ate **4b** occurs faster than that of **4a** (for details, see the Supporting Information).[14] As a model electrophile to trap the newly formed alkylmagnesium reagent we selected ethyl 2-(bromomethyl)acrylate (**6**). In initial experiments we investigated the boron–magnesium exchange reaction with trialkylboranes **2a** and **2b** (Table 1, entries 1–5), which were obtained by hydroboration of the corresponding alkene with either borane dimethyl sulfide or 9-BBN.

Table 1: Screening of organoboranes suitable for the B–Mg-exchange reaction.



Entry[a]	2	BY_2	3 (equiv)	Cosolvent[b]	Exchange time[c] [h]	Yield[d] [%]
1			**3a** (2)	Et_2O	1	81
2	**2a**[e]	$B(n\text{Oct})_2$	**3b** (2)	Et_2O	1	85
3			**3c** (2)	THF	8	n.d.
4			**3b** (1)	Et_2O	4	89
5	**2b**[e]	9-BBN	**3c** (1)	THF	8	n.d.
6			**3b** (2)	Et_2O	1	< 5
7	**2c**[e]	Bcat	**3c** (2)	THF	1	n.d.
8			**3b** (2)	Et_2O	0.5	72
9	**2d**	Bpin	**3b** (2)	THF	1	68
10			**3c** (2)	THF	0.5	93
11	**2e**		**3c** (2)	THF	1	79
12	**2f**	BF_3K	**3c** (2)	THF	6	76

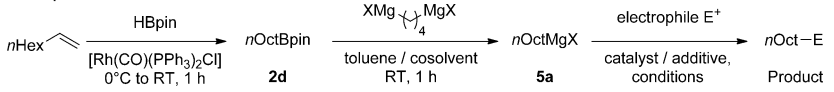
[a] Reactions were executed with 0.50 mmol organoborane. [b] Solvent, in which the dimagnesium reagent is prepared. [c] Determined by ^{11}B NMR analysis of the reaction mixture. [d] Yields of isolated alkylation products. [e] Organoborane freshly prepared in situ. *n*Hex = *n*-hexyl, *n*Oct = *n*-octyl, 9-BBN = 9-borabicyclo[4.4.1]nonane, cat = catechol, pin = pinacol, n.d. = not determined.

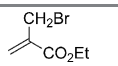
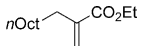
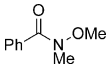
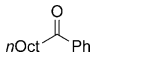
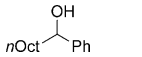
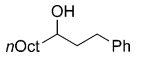
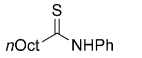
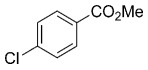
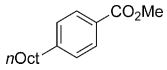
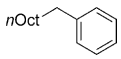
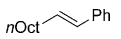
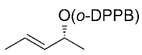
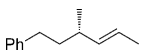
Unfortunately, even though the boron–magnesium exchange reaction employing the 1,4-dimagnesium reagent was faster, the use of a solvent mixture of toluene and diethyl ether proved necessary to achieve completion of the exchange reaction. THF, dioxane, or other polar etheral solvents that are usually used in other organomagnesium-reagent formations were not tolerated. Thus, we explored the reactivity of other types of organoboranes, mainly organoborolanes **2c–e**, which are easily prepared employing rhodium- or iridium-catalyzed hydroboration of the corresponding terminal alkene with catecholborane or pinacolborane (Table 1, entries 6–11).[15,16] While the catechol-derived organodioxaborolane **2c** failed to provide the desired alkylmagnesium reagent in solution, the reaction of *n*-octylboronates **2d** and **2e** proceeded smoothly to furnish the corresponding alkylmagnesium reagent **5a** and its subsequent alkylation product with allylbromide **6** in good to high yields. The best results were obtained for the pinacolborolane **2d**, which could be transformed into the alkylmagnesium reagent **5a** in both ether/toluene as well as THF/toluene solvent mixtures, thus enabling a greater range of subsequent addition and coupling reactions (see below Table 2).[13] Gratifyingly, even potassium organotrifluoroborate[17] **2f**, which has proven to possess a superior stability under a variety of reaction conditions[18] and potentially can be carried through several steps in a synthesis, could be employed as a substrate for the boron–magnesium exchange reaction (Table 1, entry 12). However, the limited solubility of **2f** in aprotic solvents caused the exchange reaction to be slower (6 h instead of 0.5 h for the pinacol derivative **2d**).

Next, we explored the reactivity of the newly formed alkylmagnesium reagent in a range of C–C bond forming reactions including cross-coupling reactions.[19] It was of major interest to learn whether the byproducts formed in the course of the boron–magnesium exchange reaction would have an influence on the reactivity and selectivity of the newly formed alkylmagnesium reagent (Table 2). Thus, reaction with standard electrophiles such as allyl bromide **6**, a Weinreb amide, aromatic and aliphatic aldehydes, and phenyl isothiocyanate gave high yields of the corresponding addition products; the yields were comparable to those obtained with classically prepared octylmagnesium halides (Table 2, entries 1–6).[20] When very reactive electrophiles were used to trap the alkylmagnesium reagent **5a**, lower reaction temperatures were required to avoid undesired side products derived from nucleophilic additions of the spiroboron-ate **4b**, since it is also a viable nucleophile (Table 2, entries 1, 2, and 4).[21] More interestingly, cross-coupling reactions using the alkylmagnesium reagent derived from the corresponding pinacolborolane could be carried out with success. The palladium-catalyzed Kumada cross-coupling reaction with β-bromostyrene (Table 2, entries 12 and 13) proceeded smoothly without being inhibited by the side products of the boron–magnesium exchange and occurred independently of the solvent mixture applied.[12,19] Copper-catalyzed cross-coupling[22] reactions with benzyl bromide (Table 2, entries 9–11) also proceeded in high yield. In contrast to palladium- and copper-catalyzed reactions, other cross-couplings were more strongly influenced by the byproducts of the boron–magnesium exchange process or dependent on the solvent mixture. Thus, the iron-catalyzed cross-coupling with aryl chloride[23] worked well only in THF and required a higher proportion of NMP cosolvent in comparison to the published conditions[23b] in order to achieve full conversion (Table 2, entries 7 and 8).

We were also delighted to see that we could perform the copper-mediated directed allylic substitution that was previously developed in our laboratories[24] (Table 2, entry 14).

Table 2: Scope of various electrophiles.



Entry[a]	Electrophile	Product	Dimagnesium reagent (cosolvent)	Catalyst/additive	Temp. [°C]	Solvent	Yield[b] [%]
1			**3b** (Et_2O)	–	−20	THF	83
2			**3c** (THF)	–	−20	THF	95
3			**3c** (THF)	–	0	THF	94
4			**3c** (THF)	–	−78	THF	95
5			**3c** (THF)	–	0	THF	92
6			**3c** (THF)	–	0	THF	85
7			**3b** (Et_2O)	$[Fe(acac)_3]$ (5 mol%)	RT	THF/NMP (1:1)	trace
8			**3c** (THF)	$[Fe(acac)_3]$ (5 mol%)	RT	THF/NMP (1:1)	78
9			**3b** (Et_2O)	Li_2CuCl_4 (3 mol%)	−20	THF	72
10			**3c** (THF)	Li_2CuCl_4 (3 mol%)	−20	THF	87
11			**3c** (THF)	CuCN·2 LiCl (2 mol%)	−20	THF	91
12			**3b** (Et_2O)	$[Pd(PPh_3)_4]$ (2 mol%)	RT	THF	84
13			**3c** (THF)	$[Pd(PPh_3)_4]$ (2 mol%)	RT	THF	91
14[c]			**3b** (Et_2O)	$CuBr{\cdot}SMe_2$ (0.5 equiv)	RT	Et_2O	89 (93% *ee*)

[a] Reactions were executed with electrophile (0.40 mmol), organoborane (0.50 mmol, 1.2 equiv), and dimagnesium reagent (1.0 mmol, 2.4 equiv). [b] Yields of isolated products after purification. [c] $Ph(CH_2)_2Bpin$ was used instead. NMP = *N*-methylpyrrolidone, acac = acetylacetonate, *o*-DPPB = *ortho*-diphenylphosphanylbenzoyl.

The reaction occurred with similar rates, high regio- and reliable stereospecificity as observed with classically formed alkylmagnesium reagents.

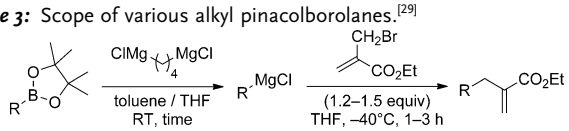
Further investigations focused on the scope of applicable alkylborolanes (Table 3). We were particularly interested in the formation of alkylmagnesium reagents that are not easily accessible in high yields by classical methods such as the alkylmagnesium reagents in benzylic and homobenzylic position (Table 3, entries 1, 2, and 9).

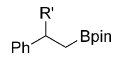
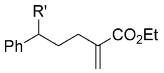
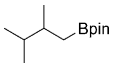
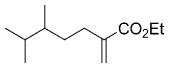
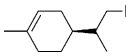
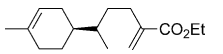
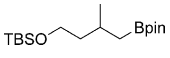
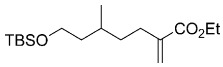
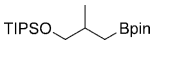
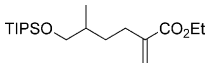
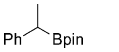
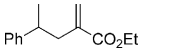
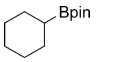
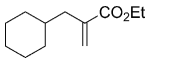
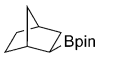
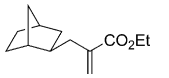
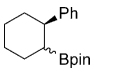
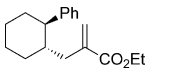
Thus, boronic esters derived from styrene derivatives and simple 1,1-disubstituted olefins could be readily transformed to the corresponding alkylmagnesium reagents in high yields (Table 3, entries 1–3). The reaction rate of the boron–magnesium exchange was found to depend on the sterical hindrance induced by the substituents next to the carbon–boron bond. While borolanes derived from monosubstituted alkenes showed a completion of the boron–magnesium exchange reaction after about one hour reaction time, the corresponding borolanes derived from 1,1-disubstituted alkenes required two to four hours for the exchange reaction to be complete. An exception was the limonene derivative, which reacted unexpectedly slow, but still gave high yields of the organomagnesium compound (Table 3, entry 4). Interestingly, this substrate possesses an additional alkene function in a 1,5-distance. Thus, preparation of the same alkylmagnesium reagent from the corresponding alkyl halide through direct synthesis is expected to furnish a bicyclic product through radical intermediates.[25] Under our conditions, the formation of such a cyclization side product could be completely suppressed.

Synthetically useful methallylalcohol- and homomethallylalcohol-derived borolanes equipped with typical silicon-based protecting groups are more sensitive substrates and required slow addition of the dimagnesium reagent at 0°C followed by slow warming to ambient temperature (see the Supporting Information) to avoid side reactions (Table 3, entries 5–8). For those sensitive substrates, 2-methyl-THF[27] instead of THF may be a superior solvent (Table 3, entry 8).

Secondary alkyl boronates derived through branched-selective hydroboration of arylalkenes or hydroboration of 1,2-disubstituted as well as trisubstituted alkenes may give access to secondary alkylmagnesium reagents provided the boron–magnesium exchange reaction could be realized at a sterically more hindered secondary alkyl carbon. To our delight, starting from the branched hydroboration product of styrene, the corresponding benzylic organomagnesium reagent was formed rather fast (4 h, Table 3, entry 9) and could be alkylated in good yield. Conversely, the cyclohexylborolane needed 16 h reaction time to reach full conversion into the corresponding alkylmagnesium reagent (Table 3, entry 10). On the other hand, the boron–magnesium exchange of the norbornylborolane (Table 3, entry 11) oc-

Table 3: Scope of various alkyl pinacolborolanes.[29]

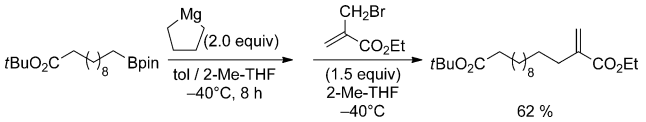


Entry[a]	Organoborane	Product	Exchange time[b] [h]	Yield[c] [%]
				
1	R′ = H		1	82
2	R′ = Me		2	76
3			2	84
4			12	71
5			4	74
6[d]			4	61
7			4	56
8[d]			4	83
9			4	86
10			16	81
11			8	68
				
12	cis/trans < 2:98	d.r. 96:4	16	76
13	cis/trans > 98:2	–	16	0
14[e]	cis/trans > 98:2	d.r. 92:8	16	61

[a] Reactions were executed with organoborolane (0.50 mmol) and dimagnesium reagent **3c** (1.0 mmol, 2.0 equiv). [b] Determined by ^{11}B NMR analysis of the reaction mixture. [c] Yields of isolated products. [d] 2-Me-THF was used instead of THF. [e] Exchange reaction was carried out at 40 °C. TBS = *tert*-butyldimethylsilyl, TIPS = triisopropylsilyl.

cured faster despite it is sterically more hindered than the simple cyclohexylborolane. The borolanes derived from a trisubstituted olefin appeared to be the greatest challenge for the boron–magnesium exchange reaction. Interestingly, with *trans*-2-phenylcyclohexyldioxaborolane (Table 3, entry 12) the exchange reaction proceeded smoothly at ambient temperature, whereas the corresponding *cis*-borolane required warming to 40 °C (Table 3, entries 13 and 14). When the resulting alkylmagnesium reagent was trapped with ethyl 2-(bromomethyl)acrylate, in both cases the *trans*-diastereomer was obtained.[26]

Finally, we explored the formation of an alkylmagnesium reagent in the presence of a reactive ester functionality. Indeed, an alkyl boronate that contained a *tert*-butyl ester was at −40 °C successfully transformed into the ester-functionalized alkylmagnesium reagent, which could be trapped by allylation (Scheme 2).



Scheme 2. Access to alkylmagnesium reagents in presence of an ester. tol = toluene.

In summary, we have developed a general protocol for the formation of a variety of primary and secondary alkylmagnesium reagents from alkenes through a sequence of hydroboration and boron–magnesium exchange with alkyl boronates allowing for clean reaction conditions, broad substrate scope, and high functional-group tolerance. The resulting alkylmagnesium reagents were useful reaction partners in a wide range of carbon–carbon bond forming reactions such as alkylation reactions, 1,2-additions as well as transition-metal-catalyzed cross-coupling reactions. Furthermore, we have demonstrated the efficiency of the boron–magnesium exchange to generate alkylmagnesium reagents that have previously only been synthesized in several steps by the established classical formation (Table 3, entries 1, 2, and 9; Scheme 2). Application of this method in total syntheses and its benefits are under investigation.

Experimental Section

Typical procedure for the formation of the alkylmagnesium reagent followed by trapping with electrophile **6**: A solution of tetramethylene bis(magnesiumchloride) (1.6–1.9 M in THF, 1.0 mmol, 2.0 equiv) was added dropwise to a cooled (0 °C) solution of the dioxaborolane (0.50 mmol) in dry toluene (1.5–2.0 mL) and the solution was stirred for the time indicated (monitored by ^{11}B NMR spectroscopy, see the Supporting Information) at ambient temperature. The reaction mixture was cooled to −20 or −40 °C, and a solution of ethyl 2-(bromomethyl)acrylate (1.4 equiv) in THF was added, and the solution was stirred for one to three hours. A saturated aqueous solution of NH_4Cl was added to the mixture, and the mixture was extracted three times with *tert*-butyl methyl ether (TBME) or diethyl ether. The combined organic phases were washed with brine, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by flash chromatography by eluting with a mixture of hexanes/diethyl ether.

Received: March 2, 2012
Published online: April 23, 2012

Keywords: boranes · C–C coupling · Grignard reaction · organoborates · synthetic methods

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